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RECEIVED 01 August 2024

ACCEPTED 18 April 2025

PUBLISHED 29 April 2025

CITATION

Del Sarto D, Masturzo L, Cavalieri A,
Celentano M, Fuentes T, Gadducci G,
Giannini N, Gonnelli A, Milluzzo G, Paiar F,
Pensavalle JH, Romano F and Di Martino F
(2025) A systematic investigation on the
response of EBT-XD gafchromic films to
varying dose-per-pulse, average dose-rate
and instantaneous dose-rate in electron flash
beams.

Front. Phys. 13:1474416.

doi: 10.3389/fphy.2025.1474416

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A systematic investigation on the response of EBT-XD gafchromic films to varying dose-per-pulse, average dose-rate and instantaneous dose-rate in electron flash beams

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Background: The FLASH effect is a radiobiological phenomena characterized by the reduction of the damage to healthy tissues while maintaining iso-effectiveness on the tumour, obtained by delivering the entire radiation dose in less than 100–200 ms and with average dose rate greater than 40–100 Gy/s. Despite the enormous interests of the scientific community, a series of issues must be addressed and overcome to reach its clinical implementation. One of these challenges is related to the dosimetry of ultra-high dose-per-pulse (UHDP) beams, which trigger the effect. The most used dosimeters to date in radiobiological experiments with ultra-high dose rate (UHDR) beams are the radiochromic films. However, a systematic and accurate study of their response by varying dose-per-pulse and dose rate over a wide range has never yet been done.

Purpose: To systematically investigate the response of EBT-XD radiochromic films under UHDR electron beam irradiations by varying different beam parameters independently and over a wide range and using flashDiamond as reference.

Materials and Methods: Thanks to a special research linac, average dose rate (ADR), dose-per-pulse (DP) and instantaneous dose rate (IDR) dependencies on film response have been individually investigated. The reference value of ADR, DP and IDR has been calculated by measuring the dose using a flashDiamond and knowing the temporal beam structure provided by the beam monitoring system of the Linac.

Results: Our results normalized to fD showed an overresponse of the radiochromic films, compared to a conventional irradiation, for ADR values higher than 1000 Gy/s and an IDR higher than 1 MGy/s which could represent a total dose overestimation of about 10%.

Discussion: The gafchromic film EBT-XD have their field of application in UHDR beam dosimetry, considering their excellent spatial resolution; However, particular attention must be paid when using this type of dosimeter for absolute dose measurements at very extreme values of IDR (>1 MGy/s).

KEYWORDS

FLASH radiotherapy, dosimetry, gafchromic films, dose-rate dependence, UHDR regime

1 Introduction

In recent years, the field of radiotherapy has undergone a significant paradigm shift with the emergence of a groundbreaking and promising modality known as FLASH radiotherapy. This innovative approach entails the administration of treatment at ultra high dose-rates (>40 Gy/s), a stark departure from conventional radiotherapy techniques with dose rates of approximately ~1–5 Gy/min. The exploration and investigation of FLASH radiotherapy have garnered substantial attention from research teams worldwide, as evidenced by a growing body of literature spanning various studies [1–4]. However, despite the growing body of evidence supporting the existence and potential clinical significance of the FLASH effect, the underlying principles governing this phenomenon remain to be discovered. To design and execute an experiment focusing on the FLASH effect, meticulous attention must be directed towards establishing robust and rigorous dosimetry protocol. This involves a comprehensive consideration of all the fundamental beam parameters associated with the FLASH effect, such as the average dose-rate (ADR), dose-per-pulse (DP), and instantaneous dose-rate (IDR) [5]. Given the extraordinary irradiation conditions requisite for triggering the FLASH effect, conventional reference active dosimeters have proven inadequate [6]. Although corrective methodologies have been proposed [7, 8] they have fallen short in meeting the exacting dosimetry requirements indispensable for radiobiological investigations. In the last years numerous research groups are actively developing specialized FLASH active dosimeters [9–13] and new methods to correct conventional active dosimeters in UHDR conditions. In this context, passive dosimeters, such as radiochromic films, maintain their field of application, considering also their very good spatial resolution [14].

Radiochromic films, widely recognized for their dose rate independence [15–19], have been widely used both in characterizing FLASH sources [5, 20, 21] and in the dosimetry of radiobiological experiments [22–24]. Despite the inconvenience of a delayed dosimetric readout spanning one to 2 days, radiochromic films have enjoyed decades of application in the realm of radiotherapy. Various well-established protocols exist, and their clinical application has undergone comprehensive scrutiny.

Moreover, the advent of deep learning techniques for image classification could speedup and simplify the employment of large batches of films [25]. Determining the response of radiochromic

films to UHDR irradiation is a relatively recent development [17, 19]. Several types of radiochromic films, including EBT3, EBT-XD, and OC1, have undergone testing with a range of UHDR sources, including pulsed electrons [17, 26] of varying energies and protons [19]. The collective evidence from these investigations suggests that radiochromic films do not exhibit a pronounced dependency on ADR, within an uncertainty margin of approximately 4% [17, 19]. However, these works have certain limitations due to the use of devices that do not allow for controlled variation of beam parameters independently of one another. Additionally, the findings have not been validated by alternative measurements using accurate dosimeters that are independent of dose rate. The present study aims to provide a comprehensive analysis of Gafchromic EBT-XD films, exploring their sensitivity to the primary beam parameters under UHDR conditions. We compare their response with measurements made using a prototype detector, which has been extensively tested and its dose rate independence verified through comparisons with DP-independent dosimeters [9].

2 Materials and Methods

The irradiations, performed using 9 MeV electron beams, were conducted at the ElectronFlash linac of the Centro Pisano for FLASH Radiotherapy (CPFR) [5], which features a unique triode gun and a dual ACCT monitoring system. Given the ability to maintain consistent irradiation setups while independently varying ADR, DP, and IDR (while preserving the same energy spectrum), this study aims to disentangle the distinct dependencies among these variables and reduce the uncertainties observed in previous studies.

2.1 Radiochromic film preparation

We employed Gafchromic EBT-XD radiochromic films (Ashland ECC), which exhibit an optimal response range when exposed to doses ranging from 0.4 cGy to 40 Gy. The films were cut into 1" x 1" squares from multiple 10" x 8" sheets, and each piece was assigned a unique number in the upper right corner to ensure consistent orientation during subsequent scans and irradiations. Our film batch was identified by the lot number 05262101. The films were stored in a tight black envelope kept in an environment with no radiation exposure. To acquire the film images, we used an Epson

10000XL flatbed scanner in transmission, whose reading panel was masked with a thick black sheet featuring a $1'' \times 1''$ aperture in the center. This was done to eliminate lateral light contributions and ensure that the same region of the flat panel captured the data, thereby minimizing scanner inhomogeneity. We configured the acquisition software to operate in positive film acquisition mode, resulting in 48-bit color images in lossless TIFF format with a resolution of 127 dpi. The scanner focus was set to 0.

Each film underwent three consecutive scans shortly before and 24 h after irradiation. While the impact of multiple scans on the film is negligible, this procedure enabled us to assess the error σ_{scan} associated with the scanner. We calculated the net optical density (netOD) for each film by analyzing the pixel values (PV) within a circular central ROI of 10 pixel radius (i.e., 2 mm radius). Each image was processed using a Wiener 2D adaptive filter to reduce noise. We calculated the netOD using the following formula (Equation 1):

$$\text{netOD} = \log_{10} \left(\frac{\text{PV}_{\text{before}}}{\text{PV}_{\text{after}}} \right) \quad (1)$$

Where $\text{PV}_{\text{before}}$ and PV_{after} the pixel values before and after the exposition of the radiochromic film to the radiation, averaged over the three repeated scans.

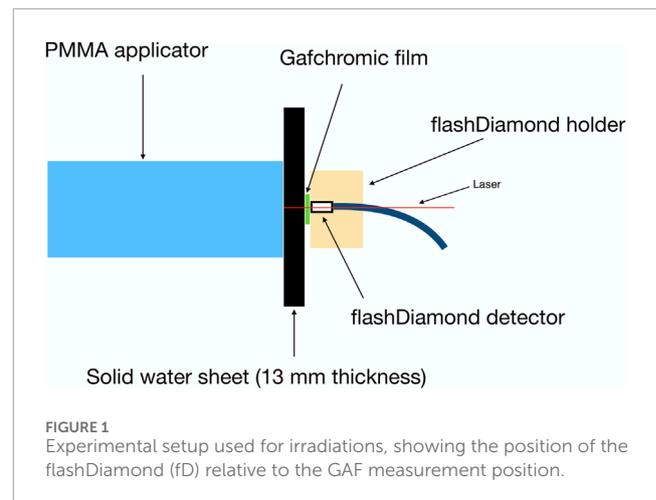
Once we characterized the beam output with the flashDiamond dosimeter, we generated a calibration curve by exposing the films to a defined range of doses, from 0.5 Gy to 60 Gy, with an ADR of 0.04 Gy/s and DP of 0.04 Gy (e-gun current of ~ 4 mA). Films were positioned at the build-up point (13 mm in solid water sheets). The choice of using directly the electron beam rather than a photon beam (from another clinical machine) was made primarily to ensure the same energy spectrum characterized with the flashDiamond. This enabled us to establish a functional relationship between the dose and the netOD through data fitting. The relationship can be expressed as:

$$D = a \cdot \text{netOD} + b \cdot \text{netOD}^n \quad (2)$$

For this first set of measurements, we used two films that were uniformly irradiated by a 100 mm diameter flat beam (flatness of 4.03% [5]), and each dose measurement was repeated twice.

2.2 Dosimetric acquisition chain

We utilized a PTW flashDiamond (fD, SN:220,439, REF:TW60025) as an additional monitoring system alongside the beam current transformers (BCTs) integrated into the linac [5]. This detector is known for its capability to function effectively under FLASH irradiation conditions without displaying significant saturation effects and has been employed in UHDR linac commissioning procedures in the past [9, 27, 28]. We also tested the fD dependence of the PRE, and its response was totally independent of it in the range of interest (1–245 Hz). The fD was connected to a PTW UNIDOS electrometer. To prevent potential issues, an external box provided by PTW was used between the diamond detector's triaxial cable plug and the electrometer's signal input. This box contained a RC circuit, which helped to smooth the current



pulses from the diamond prototype and prevent excessively high peak currents at the electrometer input [29]. This technique has been demonstrated to not produce any artifacts in the test results [27]. We positioned the EBT-XD films inside a RW3 plastic phantom at a water-equivalent depth corresponding to the R_{100} value (13 mm for a 4 mA e-gun current) obtained from the PDD (Percentage Dose Depth curve). The positioning depth of the films was kept constant, although the R_{100} value changes very slightly (by a total of ~ 2 mm) when the e-gun current is increased to 100 mA.

The plastic phantom slabs were positioned perpendicular to the beam axis. Using a workbench with adjustable solid water thicknesses, we were able to fix the setup relative to the LINAC and adjust the distance along the beam axis. Centering was achieved by precisely moving the setup closer to or further from the applicator as needed. Additionally, to ensure accurate alignment with the beam center, a laser mounted at the center of the applicator was used to align each component (solid water, GAF film, and fD).

As can be seen in Figure 1, the fD detector was positioned behind the EBT-XD film (with a 1 mm distance of the two points of measurements due to the inherent thickness of the fD(9)), precisely aligned with its center, and enclosed in a 120 mm diameter PMMA cylindrical holder. Using this configuration, we irradiated the Gafchromic films and simultaneously obtained a charge reading from the fD, allowing us to establish an alternative (to the beam monitoring system based on an ACCT signal) correlation between the film response and the beam output. Furthermore, this setup enabled us to account for any output variation from the LINAC.

2.3 Irradiation parameters

The investigation of the film response was studied varying the ADR, the DP and the IDR to assess their individual effect. Throughout the irradiations, we maintained the same amount of total dose delivered to the film and small dose variations were corrected correcting the netOD to the flashDiamond charge reading (see Equation 3). Each measurement point was repeated five times with five different films. A summary of all the irradiation conditions is reported in Table 1. We explored the dependence on the ADR using two different DP values (obtained varying the e-gun current): 3.27 Gy and 13.18 Gy. A total

TABLE 1 Irradiation conditions of the key dosimetric parameters (i.e., Average Dose-Rate (ADR), Dose-per-Pulse (DP) and Instantaneous Dose-Rate (IDR)) along with irradiation parameters (i.e., beam current and pulse duration) explored in this study.

Investigated dependency	Pulse repetition frequency (PRF)	Beam current	Pulse duration	Beam parameters
ADR	Variable intra-set [1, 80, 160, 245 Hz]	Fixed for each set	4 μ s	Variable ADR [3.64 Gy/s – 4845 Gy/s] Fixed DP [3.27; 13.18 Gy] Fixed IDR [0.82; 3.3 MGy/s]
DP	Variable [adjusted to obtain fixed ADR in the range 3.64–4845 Gy/s]	Variable [100–3.6 mA]	4 μ s	Fixed ADR [155 Gy/s] Variable DP [0.7–19.3 Gy] Variable IDR [0.18–4.82 MGy/s]
IDR	155 Hz	Variable [adjusted to obtain fixed DP]	Variable [adjusted to obtain fixed DP in the range 1–4 us]	Fixed ADR [3018 Gy/s] Fixed DP [13.0 Gy] Variable IDR [3.5–4–4.8 MGy/s]

number of 12 consecutive pulses were delivered for the lower DP setting while 3 pulses were used for the higher DP. The pulse duration was fixed (4 μ s) leading to a constant IDR for each of the two DP settings. The PRF was varied from 1, 80, 160 and 245 Hz and the explored ADR ranged from 3.56 Gy/s to 4845 Gy/s.

On the other hand, the possible dependence of the film response on the DP was investigated keeping the same total dose delivered and varying the PRF to have the same ADR of 155 Gy/s for all the irradiations, by adjusting the number of pulses. We modified the beam current to obtain seven different values of DP ranging from 0.7 Gy to 19.3 Gy. The IDR varied from 0.18 MGy/s to 4.82 MGy/s.

Finally, to investigate the possible effect of the IDR, we fixed a DP value of 13.0 Gy (obtained by changing three different beam currents and respectively adjusting the pulse duration). The pulse repetition frequency was maintained at a fixed value of 155 Hz, and the number of pulses delivered was set to three. Consequently, we obtained three distinct IDR values: 3.5, 4.0, and 4.8 MGy/s at fixed ADR (i.e., 3018 Gy/s) and DP.

3 Results

We obtained the calibration curve by fitting the measured dose as a function of the netOD using the curve presented in Equation 2. The fitting procedure accounted for uncertainties in both the netOD and the dose. The resulting calibration curve is shown in Figure 2, and the fitting parameters are presented in Table 2.

The sensitivity of the film at a given dose level was determined by performing a Taylor expansion of the function and then inverting it. For small differences in dose, we can obtain a corresponding difference in optical density using the Equation 4:

$$\Delta \text{netOD} = \frac{\Delta D}{a + b \cdot n \cdot \text{netOD}^{n-1}} \Big|_{\text{netOD}=\text{netOD}_0} \quad (3)$$

Considering that the dose delivered to the film for the netOD dependence study is about 40 Gy, a variation of 2% in dose would lead to a variation of 0.8% of the netOD.

The acquired data and the corresponding fit are presented in Figure 2.

To evaluate the influence of each irradiation parameter to the film response, we first investigated the dependence on ADR. The results of fixed total delivered dose at several ADR values and two different DP settings are shown in Figure 3. In particular, the corrected netOD (which represents the read netOD, corrected to the dose measured with the flashDiamond) as a function of the ADR for DP values of 3.27 Gy and 13.18 Gy is shown. For ADR less than about 1000 Gy/s, the response in terms of netOD (normalized to the fD charge) remained relatively constant for both DP settings, with data points fluctuating randomly. However, as ADR increased, we observed a slight (approximately 2.3%) overresponse normalized against fD, with data points consistently above the average values obtained for ADR lower than 1000 Gy/s. Given the observed slight dependence on the ADR, we conducted subsequent measurements by fixing it and investigate any other possible dependences.

Figure 4 illustrates the normalized response (against fD) of the films to varying DP for an ADR of 155 Gy/s. It is evident from the figure that the normalized netOD increases in a significant way, around 4.5%, starting monotonically from a DP of 5 Gy onward.

The data acquired at a constant DP of 13.0 Gy obtained by varying the IDR are presented in Figure 5, alongside the data obtained by converting the variable DP shown in Figure 4 into the corresponding IDR. It can be observed that there is a good agreement between the two datasets, and the difference between GAF response against fD can be seen even when only the IDR is higher than 2 MGy/s. Moreover, the magnitude of this difference (compared to fD) is consistent with the findings from previous data analysis.

4 Determination of uncertainties

Uncertainties must be determined and appropriately propagated for the following measurements:

- ADR: depends on the dose measured with flashDiamond and total irradiation time.
- DP: depends on the dose measured with flashDiamond.
- IDR: depends on the dose measured with flashDiamond and pulse duration measurement.

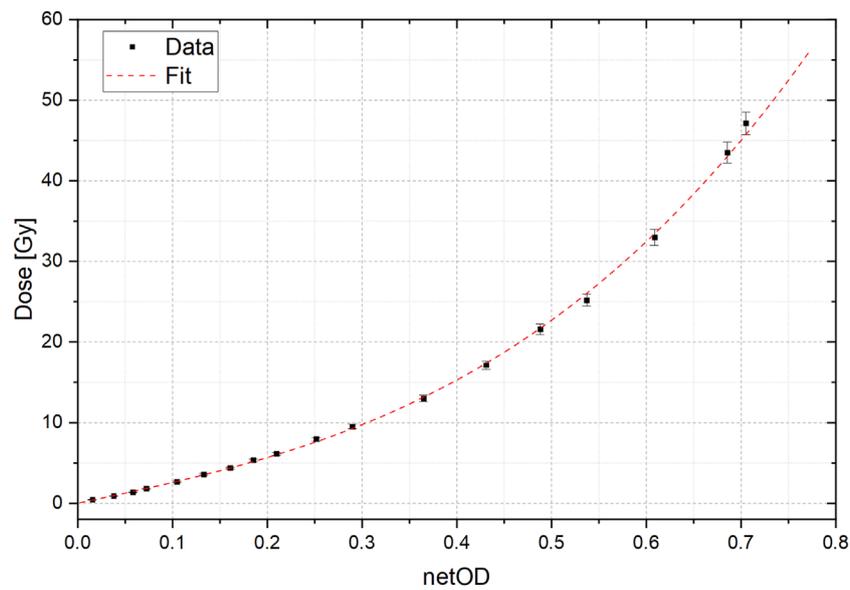


FIGURE 2 Calibration curve obtained comparing netOD values and the dose obtained using the flashDiamond. Error bars result from the uncertainty propagation of two different measurements for single dose value.

TABLE 2 Fit parameters obtained from gafchromic calibration curve.

Parameter	Value
<i>a</i>	25.0 ± 0.6
<i>b</i>	79 ± 7
<i>n</i>	2.9 ± 0.2

- OD: depends on all factors involved in processing radiochromic films.

Regarding dose measurement with the flashDiamond, literature indicates an uncertainty of approximately 3% with this detector [9]. The total irradiation time is related to the PRF, the number of pulses (n_p) and the pulse duration (t_p). Thus, ADR is given by:

$$ADR = \frac{D_p n_p}{t_p + \frac{n_p - 1}{PRF}} \approx D_p \cdot PRF \tag{4}$$

The uncertainty on ADR, if the pulse duration $t_p \ll 1/PRF$, is mainly due to the uncertainty in dose measurement. Nonetheless, if t_p is not negligible with respect to $1/PRF$, or in the case of IDR measurements, t_p is measured using on-line measurements of IDR with flashDiamond and an oscilloscope (Rigol DS1074Z Plus). In this case, the uncertainty Δt_p on t_p corresponds to the scale on the oscilloscope and can be set so that $\Delta t_p \ll t_p$, making it negligible compared to other sources of uncertainty.

Finally, we estimated OD uncertainty following the recommendations of AAPM TG 235 [30] using an estimation of about 5% for dose measurement with radiochromic films, a value consistent with previous literature [31, 32].

5 Discussion

The aim of this study was to assess the response of EBT-XD gafchromic film by independently varying the ADR, the DP and the IDR, by using the fD as reference. We found that, for a total delivered dose of about 40 Gy, there was a significant difference (~2.3%) in the netOD (normalized against the fD reading) response between low (3.56 Gy/s) and high (4845 Gy/s) ADR values. The results also show a dependence of the film response on the IDR, which was investigated up to 4.82 MGy/s. A maximum netOD overresponse (compared to the fD) between 2.5% and 6.5% was found for the extreme IDR of 4.82 MGy/s when compared with IDR of 2 MGy/s. If future studies validate the use of fD as a reference, our finding implies a not negligible corresponding maximum dose overestimation of $7\% \pm 3.3\%$ for a dose of 40 Gy obtained applying the dose calibration performed at low ADR and IDR conditions. The obtained data suggest that there are two contributing factors to the netOD overestimation. The first factor is linked to the ADR, which was evaluated for two different DP. Though not statistically significant, we observed an increasing trend from an ADR exceeding 1500 Gy/s up to approximately 5,000 Gy/s. The second factor is dependent on the IDR where the effect begins to manifest starting from around 1.5 MGy/s. The study of the IDR dependence was executed at an ADR of 3018 Gy/s, hence higher than the value found with the overresponse linked to the ADR. Given the irradiation conditions the two dependencies can be deemed independent.

The overall uncertainties in the irradiations were minimized thanks to the ElectronFlash linac that enabled us to maintain the same experimental setup and energy spectrum. We also verified, through a calibration curve executed with conventional irradiation parameters, that the selected dose value was within the optimal range of the film's response, excluding phenomena

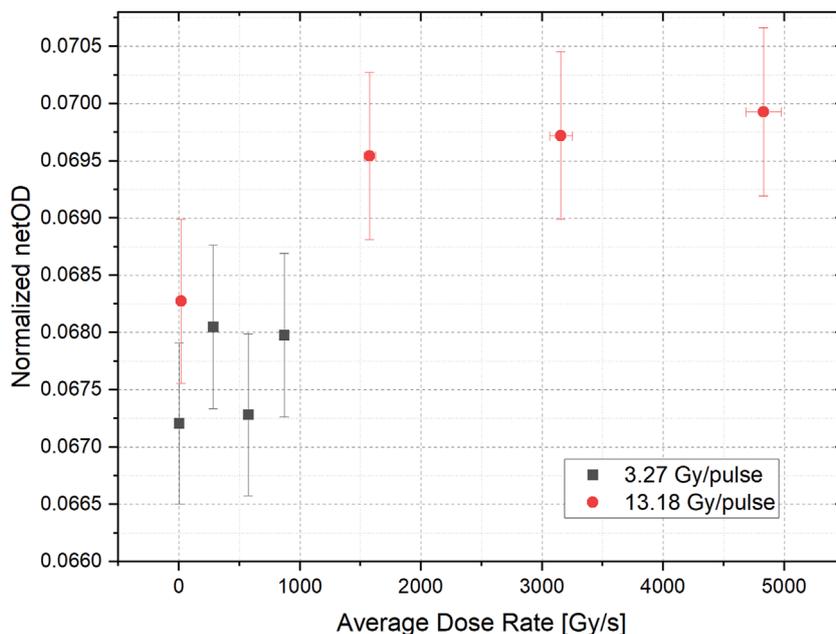


FIGURE 3 Normalized netOD to fD charge for two different dose-per-pulse values (3.27 Gy in black and 13.18 Gy in red) in function of the average dose-rate (ADR). Error bars result from the error propagation of netOD and dose obtained from fD.

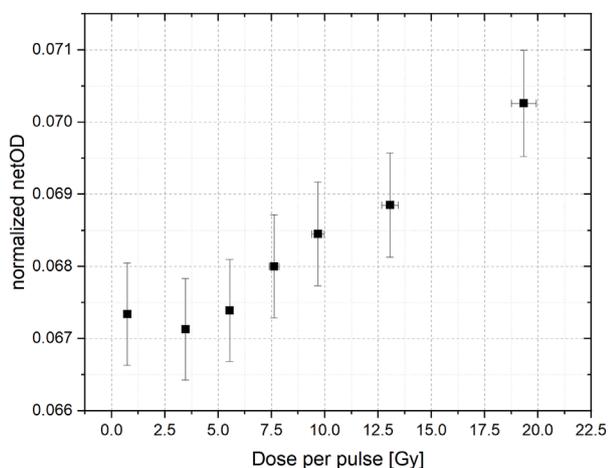


FIGURE 4 Normalized netOD to fD charge in function of the dose-per-pulse. Error bars result from the propagation. Error bars result from the error propagation of netOD and dose obtained from fD.

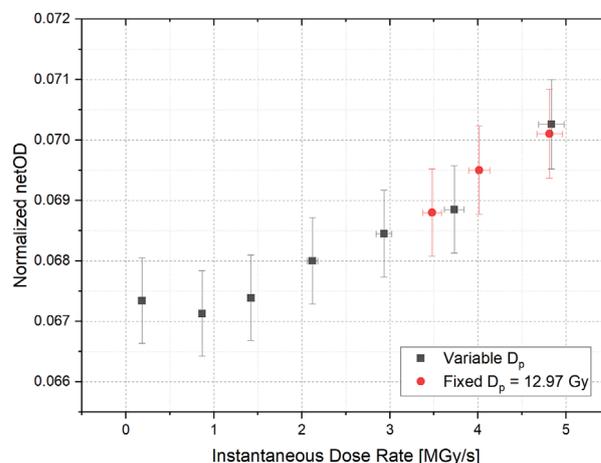


FIGURE 5 Normalized netOD to fD charge in function of the instantaneous dose-rate for a fixed dose-per-pulse (12.97 Gy in red) and variable dose-per-pulse (in black). Error bars result from the error propagation of netOD and dose obtained from fD.

linked to non-standard working conditions. This is consistent with the manufacturer specification and several other studies [33]. Any minor dose variations from the nominal one caused by delivery fluctuations were measured using as monitoring device the same dosimeter used for the reference dosimetry, the flashDiamond, and the resulting netOD was corrected accordingly.

Previous studies have already examined the response of radiochromic films to various beam parameters and concluded

that gafchromic films do not exhibit any differences in their response for irradiation conditions. However, in Jaccard et al., the films were irradiated with uneven dose values and compared through the calibration curve [17]. This approach could mask low entity dependency (below 5%) due to the increased uncertainty associated with the conversion of netOD values to dose values and the inherent uncertainty associated with selecting the appropriate irradiation condition for the calibration curve. As a result, we

conducted our analysis directly on the netOD values to avoid these shortcomings.

More extreme irradiation condition (up to 10^9 Gy/s) were tested in Karsch et al. [15], but again, the comparison was made through the calibration curve (obtained at completely different setup from the one of the study). Meanwhile, a more recent study by Guan et al. [16] asserted that no dose rate dependence was found, but their study was limited to a maximum dose rate of 150 Gy/s. More recently, a study from Villoing et al. [19], started to observe an overresponse of the EBT-XD film to higher ADR and IDR (7500 Gy/s), but they were unable to test the response of the films to individual beam parameters. Our study is subject to certain limitations that warrant consideration.

The study would have been conceptually more precise by reconstructing complete dose-optical density curves across varying beam parameters (ADR, DP, IDP). However, this approach would be overly labor-intensive and practically unfeasible due to the totally different dosimetric steps across different DPs. Instead, we decided to fix the dose level for the irradiations, which allowed us to vary the parameters we wanted to investigate in an extreme manner. We then demonstrated that, for dose variations within 2% (the maximum variation recorded in our data), the resulting change in netOD is negligible and we applied a correction for minor dose variations. While not optimal, since the calibration curve parameters can shift with beam parameters, this correction is certainly more accurate than a linear approximation or no correction at all.

Our decision to focus exclusively on a single type of radiochromic film (EBT-XD) was predicated on its perceived suitability due to its more appropriate dose range response for FLASH irradiation, spanning up to 40 Gy. In contrast, the optimal dose range of EBT-3 (0.2–10 Gy) could potentially prove restrictive in certain extreme FLASH settings necessitating DP values exceeding the 10 Gy threshold. Consequently, opting for EBT-XD enabled us to operate within the optimal range delineated for the film's efficacy (0.4–40 Gy) and consequently have a superior response compared to the EBT3 film.

In our investigation, a uniform dose of approximately 40 Gy was administered across all films. This was motivated by our goal to create the most extreme irradiation conditions achievable within the operational limits of the linac, while independently manipulating the beam parameters. While existing studies suggest that observable effects may not emerge until doses reach 30 Gy [19], our decision to deliver higher doses was also informed by the potential insights that could be gained at higher values.

Further steps will be made to extend the results of this study to more extreme irradiation conditions and different beam energies. In conclusion, we advise caution when employing these films for absolute dosimetry within FLASH conditions—both in the context of FLASH source commissioning and radiobiological experiments.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. LM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. AC: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. MC: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. TF: Methodology, Validation, Visualization, Writing – review and editing. GG: Methodology, Validation, Visualization, Writing – review and editing. NG: Methodology, Validation, Visualization, Writing – review and editing. AG: Visualization, Writing – review and editing, Methodology, Validation. GM: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – review and editing. FP: Funding acquisition, Methodology, Validation, Visualization, Writing – original draft. JP: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review and editing. FR: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review and editing. FD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was funded by European Union - Next Generation EU, Mission 4 Component 2 Inv. 1.5, ECS00000017 “Ecosistema dell’innovazione” Tuscany Health Ecosystem (THE), Spoke 1 “Advanced Radiotherapies and Diagnostics in Oncology”—CUP I53C22000780001.

Acknowledgments

We thank Fondazione Pisa for funding CPFR with the grant “prog. n. 134/2021”.

We also thank Minibeam Radiotherapy (MIRO) INFN project for scientific collaboration.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of *Frontiers*, at the time of submission. This had no impact on the peer review process and the final decision.

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